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A change in estimate procedure for multiple level exposure and binary outcomes: a backward approach

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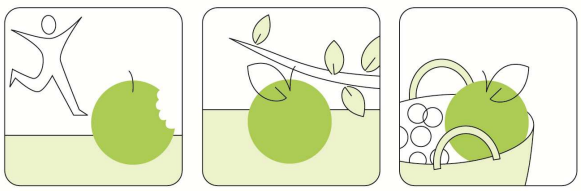

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This report was prepared by:

Danilo Fusco, Anna Patrizia Barone, Paola Colais (partner DEASL[1])

[1] Department of Epidemiology ASL Roma E, Italy

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Background

When conducting a non-experimental study, investigators must try to identify and control variables that could confound estimation of the exposure effect on outcome or outcome frequency. In these cases, the main problem is setting the criteria for choosing these variables, which is necessary to provide valid estimates of exposure effects.

The inclusion within a risk adjustment model of factors that do not actually induce a relevant bias in the estimate of the measure of association may cause a loss of precision and implies additional costs of collecting the relevant information. Therefore the selection of the "best" risk adjustment models should aim to the maximum parsimony.

Commonly used confounder selection criteria have been classified into five categories [1].

Category 1 criteria involve adjusting for all measured variables. This strategy may not be viable if there are many potential confounders. Collecting many variables, apart from being onerous, usually entails problems with data completeness, accuracy, and reliability and tends to reduce the precision of the adjusted measures [2-5].

For category 2 criteria, the goal is adjusting for a variable only if its association with the outcome of interest is statistically significant at some preset level [5,6]. This strategy is commonly based on stepwise regression methods.

Category 3 criteria involve adjusting for a variable only if its control produces a statistically significant change in the exposure-effect estimate [7].

Category 4 criteria address adjusting for a variable unless its control produces a change in the exposure-effect estimate statistically equivalent to zero [8].

Category 5 criteria target adjusting for a variable only if its control exceeds a cut-off percentage of change in the exposure-effect estimate [2,5] (e.g., a 10% or 20% change in the risk ratio of interest). However, the choice is arbitrary; the relevance of the observed confounding effect must be appraised in relation to the study specific aim, design and utilization of the study results. This strategy is called "change-in-estimate" (CE). It improves parsimony of the model and gains precision of the estimates, by eliminating variables that are not actual confounders.

The CE approach is usually implemented in a stepwise manner [2]: as variables are added or removed from a regression model, the procedure selects confounding variables according to the amount of change in the estimate of exposure observed. For example, following a backward approach, among all variables entered in a model, the CE procedure finds the variable that, if deleted, would cause the smallest change in the estimated

exposure effect. If this change is lower than a preset amount, the variable is deleted from the model because it is considered to have no substantial confounding effect.

A limit of this procedure is that the confounders can be identified only for dichotomous exposures, not for multiple level exposures. Some statistical software programs offer different algorithms to perform the CE procedure for dichotomous exposures [9,10,11]. The Department of Epidemiology of ASL Roma E has developed, by a SAS macro, an approach that overcomes the limits of the traditional methodology, allowing selection of confounders for multiple level exposure.

Methods

The procedure developed in SAS has been tested on an Acute Myocardial Infarction (AMI) cohort. The outcome of interest was in-hospital mortality within 30 days from the first hospital admission (index admission) for an AMI episode. All potential risk factors were retrieved from the Health Information System using the discharge diagnoses of previous hospital admissions during the last 24 months (see Appendix A). Two different exposures were considered: (1) hospitals of treatment, used as an example of several categories of exposure; and (2) education levels (≤ 5, 6–8, ≥ 9 years), used as an example of three categories of exposure.

***Selection of risk factors*.** Among all factors potentially associated with the outcome under study and identified by a literature review, some factors were considered *a priori* as risk factors; the others were selected by a stepwise procedure (level of significance of 0.05, exclusion probability of 0.10, and inclusion probability of 0.05).

***Identification and selection of confounders*.** The identification and selection of confounders were performed using the following steps:

1. A multivariate regression model (“full model”) was constructed including the exposure of interest and the *a priori* and the *selected* risk factors. The exposure effect estimates from the full model were selected as being the most valid obtainable estimates (gold standard).
2. The exposure effects were estimated for the models obtained excluding one *selected* risk factor at a time.

3. For each exposure category, the percent absolute variation between the exposure effect estimated by the full model and that estimated by each model from the previous step was calculated. For each model, the maximum variation is identified.
4. After these maximum variations were ranked, the *selected* risk factor associated with the lowest maximum variation was excluded.
5. Starting from the remaining risk factors, steps 2–4 were repeated, until all selected risk factors were deleted.
6. Among all models run, only models with a maximum absolute variation lower than a preset cut-point (10%) were selected, and the model including the lowest number of variables was considered to be the "parsimonious" one.

The exposure effect was estimated by ORs (odds of 30 day in-hospital mortality for an exposure category vs. odds of death for the reference category) using logistic multivariate regression models.

To compare the precision of exposure effect estimates between the full and the parsimonious models, the standard errors were also compared.

The statistical analysis was performed using SAS Version 8.02 [10]. A SAS macro was created and tested to perform the algorithm and is available to all Euphoric partners on request.

Results

A cohort of 23,594 incident events of AMI was enrolled according to selection criteria. Table 1 shows the number of admissions for AMI and the 30 day in-hospital mortality for all potential risk factors. Crude and adjusted OR estimates and their statistical significance (p value) are presented only for the *a priori* and the *selected* risk factors, identified by a stepwise procedure.

The full model included age and gender as *a priori* risk factors. *Selected* risk factors were malignant neoplasms, diabetes without complications, previous AMI, congestive heart failure, chronic vascular and cerebrovascular disease, chronic renal disease, previous coronary artery bypass graft, and previous percutaneous transluminal coronary angioplasty.

When hospital of treatment was used as an exposure, the SAS procedure identified as parsimonious a model that included only three confounders (two *a priori* and one *selected* risk factors): age (OR = 1.08, $p < 0.001$), gender (OR = 1.01, $p = 0.795$), and

chronic renal disease (OR = 2.10, p < 0.001). Some important predictors of outcome, included in the full model, such as congestive heart failure and chronic vascular and cerebrovascular disease, were excluded from the parsimonious one because they were homogeneously distributed among hospitals.

When using education levels (years) as an exposure, the SAS procedure identified as parsimonious the model that included only the two *a priori* risk factors: age (OR = 1.08, p < 0.001) and gender (OR = 0.98, p = 0.603).

Table 2 and table 3 show, by hospital and education level (years), the number of AMI index admissions, the mortality rates, the crude and adjusted ORs estimated by using the full and the parsimonious models, and their 95% confidence intervals. In table 2, the reference category includes the hospitals with the lowest adjusted mortality rates based on the full model.

For the two exposures, the CE procedures yielded ORs substantially similar to those obtained from the full models, but the estimates from the parsimonious models were more precise than those from the full models.

Discussion

The CE is a method that improves the parsimony of a model and gains precision of the estimates by identifying variables that are confounders. Following a backward approach, confounders are defined as variables that, when excluded from the models, change the exposure effect estimate (i.e., comparison of adjusted OR with or without those variables) by a percentage arbitrarily chosen (usually from 10% to 20%).

To determine the relevance of the confounding effect, it must be appraised relative to the specific aim, study design, and application of the study results. Precision can be lost with the inclusion of factors within a risk adjustment model that do not induce a relevant bias in the estimate of the measure of association. Therefore, the selection of the “best” risk adjustment model should target maximum parsimony [14].

In our simulation, among the 11 outcome predictors selected by a stepwise procedure and included in the full model, only three risk factors were heterogeneously distributed among the hospitals, and two factors seemed to act as confounders in the comparison of education levels.

A limit of the CE approach is that the confounding variables can be identified only for dichotomous exposures. An attempt to overcome this problem was presented in a study in which the traditional CE procedure was applied to an exposure with multiple categories

[15]. In that case, the CE procedure was repeated for comparing each category of exposure and the reference one, defining as many models as there were comparisons. Confounders were identified through single comparison. The “best possible compromise” between the demands of parsimony and making valid multiple comparisons was to run a single model including each confounding variable represented in at least one comparison along with the multiple level exposure [15].

However, if there were several categories to compare, this solution could be too onerous in terms of time and calculation complexity [14]. Moreover, these confounders are selected by different risk adjustment models applied to different populations, one for each exposure category; thus, this strategy might lead to the identification of confounders that are not representative of the overall change in the exposure variable.

The CE procedure presented in this document provides an alternative to currently available confounder selection methods, identifying confounders for dichotomous and multiple exposures. Because they are selected by risk adjustment models applied to the whole population being studied, confounders selected by simultaneous comparison of all categories of exposure and the reference one are representative of the overall change in the exposure variable (dichotomous or multiple).

Another limit of the traditional methodology is that the percent variation of the exposure effect, estimated at a given step, is calculated from models including or excluding the potential confounder under evaluation. This criterion could result in some confounders not being identified. Consider, for example, 15 non-correlated potential confounders to be evaluated by a traditional CE procedure. Assuming a cut-point of 10%, if the exclusion of each potential confounder from the model induced an independent reduction of about 1% in the exposure effect, the CE would identify no confounders. In fact, at each step, in a comparison of the exposure effect estimates from two models with or without the potential confounder under evaluation, the variation of exposure would be about 1%.

The SAS procedure developed overcomes this limitation because at each step, the variation is calculated relative to the full model. In the example in the previous paragraph, this procedure would identify the last five factors as confounders; in fact, the exclusion of the 11^{th} factor would imply a variation of 11%.

The maximum percent absolute variation was chosen as a criterion to identify the confounders. It was defined as the maximum variation of exposure effects among the variations calculated for each exposure category. The maximum is a statistic more

sensitive than geometric mean or cumulative sum in detecting high variations in at least one category of exposure; therefore, it could lead to the detection of more confounders than the other statistics. This outcome, however, should be true only for multiple exposures, with no differences identified in the detection of confounders for dichotomous exposures.

A potential source of criticism for CE strategies is that they take no account of random variability in the coefficient estimates being compared [5,16]. In addition, the selection of the cut-point used to identify the confounders can be problematic. However, as demonstrated in previous studies, setting the cut-point to a low level (10%) seems to ensure a good performance of this strategy [1,5,6,16].

Conclusions

The change-in-estimate procedure presented in this document has been developed to overcome the limits of the traditional methodology, allowing selection of confounders of an exposure-outcome association in the case of multiple exposures. In addition, it targets identification, among all developed models, of the most parsimonious model that provides more precise estimates without compromising validity.

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Table 1. Index AMI admissions, mortality (%), crude ORs, adjusted ORs from the full model and statistical significance, by risk factor

Risk factors	n	mortality (%)	crude OR	p-value	adjusted OR full	p-value
Age	-	-	1.08	0.000	1.08	0.000
Gender (female vs male)	8146	15.9	1.79	0.000	0.99	0.760
Malignant neoplasms	1091	20.4	2.01	0.000	1.60	0.000
Diabetes with acute and chronic complications	780	18.1				
Diabetes without complications	2275	16.6	1.57	0.000	1.19	0.012
Lipid metabolism disturbances	957	8.3				
Obesity	219	12.8				
Blood disorders	785	24.1				
Hypertension	4127	14.8				
Previous myocardial infarction	3469	10.8	0.90	0.077	0.71	0.000
Chronic ischemic heart disease	3248	14.7				
Congestive heart failure	1446	22.0	2.27	0.000	1.23	0.008
Ill-defined descriptions and complications of heart disease	695	22.9				
Rheumatic heart disease	170	24.7				
Cardiomyopathy	364	19.5				
Acute endocarditis and myocarditis	13	30.8				
Other heart conditions	307	17.3				
Cardiac arrhythmias	1735	19.8				
Chronic cerebrovascular disease	1505	21.4	2.19	0.000	1.31	0.000
Chronic vascular disease	1038	19.8	1.93	0.000	1.27	0.008
Chronic obstructive pulmonary disease (COPD)	1510	20.0				
Chronic renal disease	1010	26.6	2.92	0.000	1.90	0.000
Other chronic disease (liver, pancreas, intestine)	277	16.6				
Coronary Artery Bypass Graft (CABG)	1056	4.7	0.36	0.000	0.48	0.000
Percutaneous Transluminal Coronary Angioplasty (PTCA)	1424	5.1	0.39	0.000	0.58	0.000
Endarterectomy	149	14.8				
Other operations on heart and pericardium	73	16.4				
Other operations on vessels	355	19.2				

Table 2. Index AMI admissions, mortality (%), crude ORs, adjusted ORs and 95% confidence intervals, calculated by using the full and the parsimonious model, by hospital of treatment

Hospitals of treatment	n	mortality (%)	crude OR	95%CI	adjusted OR full	95%CI	adjusted OR parsimonious*	95%CI
Ref	2382	7.3	-	- -	-	- -	-	- -
00700	172	9.3	1.29	0.76 - 1.83	1.31	0.76 - 1.87	1.37	0.81 - 1.92
01900	830	12.0	1.73	1.47 - 1.99	1.37	1.10 - 1.64	1.43	1.16 - 1.70
02601	809	9.9	1.38	1.11 - 1.66	1.14	0.85 - 1.43	1.12	0.83 - 1.41
02700	279	10.4	1.46	1.05 - 1.88	1.20	0.77 - 1.64	1.23	0.79 - 1.66
04500	360	10.6	1.49	1.12 - 1.86	1.31	0.92 - 1.69	1.39	1.01 - 1.78
04600	408	10.5	1.49	1.13 - 1.84	1.29	0.92 - 1.66	1.31	0.94 - 1.67
04700	585	8.5	1.18	0.85 - 1.51	1.26	0.92 - 1.60	1.20	0.86 - 1.54
05300	676	15.1	2.24	1.98 - 2.50	2.02	1.74 - 2.29	2.09	1.82 - 2.36
05400	202	12.9	1.86	1.42 - 2.30	1.25	0.79 - 1.71	1.29	0.83 - 1.75
06100	718	9.6	1.34	1.05 - 1.63	1.16	0.85 - 1.46	1.17	0.87 - 1.47
06600	720	14.0	2.06	1.80 - 2.32	1.99	1.72 - 2.27	2.03	1.76 - 2.31
07100	448	14.7	2.18	1.88 - 2.48	2.60	2.28 - 2.92	2.53	2.21 - 2.85
07600	636	10.2	1.44	1.14 - 1.73	1.22	0.91 - 1.53	1.25	0.94 - 1.56
13400	338	9.5	1.32	0.92 - 1.71	1.82	1.41 - 2.23	1.83	1.42 - 2.24
16500	753	12.1	1.73	1.47 - 2.00	1.86	1.58 - 2.14	1.79	1.51 - 2.07
17100	325	10.8	1.52	1.14 - 1.91	1.41	1.01 - 1.80	1.34	0.94 - 1.73
18000	529	11.9	1.70	1.40 - 2.01	1.69	1.37 - 2.01	1.72	1.40 - 2.04
20001	945	12.0	1.71	1.46 - 1.96	1.90	1.64 - 2.16	1.93	1.67 - 2.19
21500	158	18.4	2.84	2.40 - 3.27	3.61	3.14 - 4.07	3.76	3.30 - 4.23
21600	764	9.3	1.29	1.00 - 1.58	1.48	1.18 - 1.78	1.47	1.17 - 1.77
22600	270	11.1	1.58	1.17 - 1.99	1.65	1.22 - 2.08	1.69	1.27 - 2.12
22800	300	8.0	1.10	0.65 - 1.54	1.24	0.78 - 1.70	1.28	0.82 - 1.74
26700	1491	15.4	2.30	2.09 - 2.51	2.29	2.07 - 2.51	2.28	2.06 - 2.49
27100	777	10.3	1.45	1.17 - 1.73	1.50	1.21 - 1.79	1.51	1.22 - 1.79
90100	1656	12.6	1.82	1.61 - 2.03	1.64	1.42 - 1.86	1.64	1.42 - 1.86
90200	1175	13.6	1.99	1.76 - 2.21	1.81	1.57 - 2.05	1.81	1.57 - 2.05
90301	1093	8.6	1.19	0.93 - 1.45	1.31	1.04 - 1.59	1.23	0.96 - 1.50
90501	865	10.8	1.52	1.25 - 1.78	1.56	1.28 - 1.84	1.57	1.29 - 1.85
90600	962	12.8	1.85	1.60 - 2.09	1.93	1.67 - 2.19	1.98	1.72 - 2.23
92000	152	8.6	1.18	0.59 - 1.77	1.31	0.69 - 1.93	1.25	0.63 - 1.87

Ref: reference hospitals

* adiusted for the actual confounders: age, gender and chronic renal disease

Table 3. Index AMI admissions, mortality (%), crude ORs, adjusted ORs and 95% confidence intervals, calculated by using the full and the parsimonious model, by educational level

Educational level (years)	n	mortality (%)	crude OR	95%CI	adjusted OR full	95%CI	adjusted OR parsimonious*	95%CI
<=5	11536	15.6	-	- -	-	- -	-	- -
6-8	7366	8.7	0.51	0.42 - 0.61	0.99	0.88 - 1.09	0.97	0.87 - 1.07
>=9	4692	6.9	0.40	0.28 - 0.52	0.84	0.71 - 0.98	0.82	0.69 - 0.96

* adiusted for the actual confounders: age, gender

Appendix A: List of potential risk factors searched in previous admissions. ICD-9-CM and ICD-10 codes

Risk factors	ICD-9-CM Code	ICD-10 Code
Malignant neoplasms	140.0–208.9	C00- C96
Diabetes with acute and chronic complications	250.1-250.9	E10-E11 (excluding E10.9 and E11.9)
Diabetes without complications	250.0	E10.9, E11.9
Lipid metabolism disturbances	272	E78
Obesity	278.0	E66
Blood disorders	280-285, 288, 289	D50-D53, D55-D64, D70-D77, D80-D89
Hypertension	401-405	I10-I15
Previous myocardial infarction	410, 412	I21, I22, I25.2
Chronic ischemic heart disease	411, 413, 414	I20, I24, I25.1, I25.3–I25.9
Congestive heart failure	428	I50
Ill-defined descriptions and complications of heart disease	429	I51
Rheumatic heart disease	391, 393-398	I00-I02, I05-I09
Cardiomyopathy	425	I42-I43
Acute endocarditis and myocarditis	421, 422	I33, I40-I41
Other heart conditions	745, V15.1, V42.2, V43.2, V43.3, V45.0	Q20, Q21, Q25, Z95.2-Z95.4, Z94.1, Z95.81
Cardiac arrhythmias	426, 427	I44-I49
Chronic cerebrovascular disease	430-434, 436-438	I60-I67, I69
Chronic vascular disease	440-448, 557	I70-I74, I77-I78, K55
Chronic obstructive pulmonary disease (COPD)	491-492, 494, 496	J41-J44, J47
Chronic renal disease	582-583, 585-588	N03, N05, N11, N12, N18, N19, N25-N27
Other chronic disease (liver, pancreas, intestine)	571-572, 577.1-577.9, 555, 556	K70, K71 K72.1, K72.9, K73-K76 (excluding K71.2, K76.1-K76.4), K86, K50, K51
Previous aortocoronary bypass graft	36.1, V45.81	Z95.1, Procedure code
Previous Percutaneous Transluminal Coronary Angioplasty (PTCA)	36.0, V45.82	Z95.5, Procedure code
Operations of intracranial and other vessels of head and neck, including	38.01, 38.02, 38.11,	Procedure codes

endarterectomy	38.12, 38.31, 38.32	
Other operations on heart and pericardium	35, 37.0, 37.1, 37.3, 37.4, 37.5, 37.6, 37.9	Procedure codes
Other operations on vessels	38-39.5, excluding: 38.01, 38.02, 38.5, 38.11, 38.12, 38.31, 38.32, 38.93	Procedure codes